Methamphetamine
Stimulant of the 1990s?

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During the past several years, the use of a smokable form of methamphetamine hydrochloride called "ice" has increased rapidly. The heaviest use has occurred on the West Coast and in Hawaii. Many regional emergency departments treat more methamphetamine users than cocaine-intoxicated patients. The ease of synthesis from inexpensive and readily available chemicals makes possible the rampant abuse of a dangerous drug that can produce a euphoria similar to that induced by cocaine. Clinicians should be familiar with the medical effects and treatment of acute methamphetamine toxicity.

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A dramatic increase has occurred in the illicit production and use of methamphetamine hydrochloride (HCl) over the past several years (M. Glover, "State Production of Speed Worries U.S. Drug Officials," *Sacramento Bee,* October 10, 1988, p1).[1-3] Endemic areas for this increase include the Pacific Coast states and Hawaii.[4] In 1987 in San Diego County, California, methamphetamine intoxication played a role in 40% of all drug-related homicides.[5] This represents a 52% increase in methamphetamine involvement in serious crime over the previous year. In San Bernardino County, California, the number of coroners' cases involving methamphetamine use has been twice that of cocaine.[6] At present, this epidemic appears confined to the West Coast where in some emergency departments, the number of visits resulting from methamphetamine intoxication exceeds that necessitated by cocaine use.[6,7] Although data from the National Institute on Drug Abuse indicate that cocaine abuse is still greater than that of methamphetamine, the new trend is of great concern.[8]

Methamphetamine provides a euphoria similar to that of cocaine.[9] Studies in animals have shown that methamphetamine and cocaine induce similar behavior.[10] The smokable form of methamphetamine ("ice") can bring on an immediate euphoria with effects that may last many times longer than those of cocaine.[4] Methamphetamine abuse involves a wide age range, and epidemic methamphetamine abuse has recently been described in adolescents. In one inpatient adolescent drug treatment unit, methamphetamine was listed as the drug of choice by about 80% of patients recently admitted.[1] The reasons given for this preference include availability, low cost, and a longer duration of action compared with cocaine. Both oral and intravenous use are well documented, but the use of smokable methamphetamine has received little attention in medical literature.

History

Amphetamine was introduced in the 1930s in the form of inhalers for treating rhinitis and asthma.[11] The stimulant, euphoriant, and anorectic effects of amphetamine were quickly recognized, leading to its abuse. A report in 1937 stating that amphetamine could enhance intellectual performance through enhanced wakefulness further contributed to amphetamine abuse.[12] Amphetamine was used by some foreign armies during the Second World War, allegedly to increase wakefulness and attention.[13] After the mid-1940s, epidemics of amphetamine abuse occurred in several countries, most notably Japan and Sweden. Initial federal controls were enacted in the late 1950s, but amphetamine continued to be abused by some students, athletes, shift workers, and truck drivers into the next decade.[14] The Controlled Substance Act of 1970 stringently regulated the manufacturing of amphetamine. As a result, the availability of dextroamphetamine sulfate (Dexedrine) and other pharmaceutical amphetamines decreased. Despite the declining availability of pharmaceutically synthesized amphetamines, methamphetamine use has increased notably.

Illicit Production

Unlike D-amphetamine, methamphetamine is easy to synthesize in a crude laboratory.[15] Like other sympathomimetic drugs, both are derivatives of phenylethylamine. Structurally, the substances differ in that a methyl group attaches to the terminal nitrogen of methamphetamine. Although some states have enacted laws decreasing the availability of necessary precursor chemicals,[16] these agents may still be obtainable in neighboring states.

One common method of synthesis begins with L-ephedrine, which is reduced to methamphetamine using hydriodic acid and red phosphorus.[17] Variations on this process include using a different acid or catalyst or a substituted ephedrine such as chloroephedrine or methylephedrine. The product is pure D-methamphetamine, which is several times more active than the L form. The ephedrine reduction process is responsible for more than 90% of the methamphetamine produced in southern California (P. Gregory, Drug Enforcement Administration, Sacramento, California, oral communication, November 1988). The methamphetamine produced is a lipid-soluble pure base form, which is volatile and evaporates if left exposed to room air. The producer, therefore, uses hydrochloride to

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
HCl = hydrochloride
MDMA = methylenedioxymethamphetamine

convert it to the water-soluble form, methamphetamine-HCl powder. This substance has traditionally been sold on the street as "speed," "crank," "go," "crystal," or methamphetamine, and it is highly water soluble.

Other stimulants such as cocaine, phenylpropanolamine hydrochloride, D-amphetamine, ephedrine, or pseudoephedrine have been mixed with or substituted for methamphetamine. Several years ago, street methamphetamine was highly impure and found in only 40% of the street-purchased drug.[18] More recent information from law enforcement laboratories suggests that the methamphetamine available now is nearly pure.[6] Some clandestine chemists purposely produce other stimulants with toxicity of their own, which may be sold as methamphetamine. These stimulants structurally resemble methamphetamine and include methylenedioxymethamphetamine (MDMA), methylenedioxyamphetamine (MDA), 2,5-dimethoxy-4-methylamphetamine (DOM), and bromodom (DOB) and have been referred to as "designer drugs."[19] The routine toxicologic screen may not detect many of the new congeners, such as MDMA, and the drugs may produce symptoms indistinguishable from those induced by methamphetamine.[20,21] Illicitly synthesized methamphetamine may be contaminated by nonstimulant organic or inorganic substances. Lead poisoning and exposure to carcinogenic material have been reported.[22] Street methamphetamine may be mixed with cocaine, and studies show that 8% to 20% of street-available stimulants contain both drugs.[18] In a recent report on cocaine intoxication, 7% of patients sought medical help because of the concurrent use of cocaine and amphetamines.[23]

Ice

The term "ice" originated in the Far East as the result of synthesizing large crystals of methamphetamine through the ephedrine-reduction method (M. Corwin, "Potent Form of Speed Could Be the Drug of '90s," *Los Angeles Times*, October 8, 1989, p1). Once the methamphetamine HCl is produced, making ice involves a process analogous to making rock candy out of sugar. The methamphetamine HCl is slowly added to water, heated to 80°C to 100°C until a supersaturated solution is obtained, and the slurry is then cooled. The pure HCl salt of methamphetamine, also known as ice, precipitates from this. Isopropanol has been used as the solvent in place of water. The many variations of this process result in an unreliable removal of impurities. Many physical characteristics of the final product depend on the quality of the reagents and on the contaminants. Unlike cocaine HCl, methamphetamine HCl is volatile and can be smoked.[24] For cocaine to be smoked, it must be converted to pure cocaine alkaloid, commonly called crack (Table 1).

TABLE 1.—*Comparison of Methamphetamine and Cocaine*

Common Street Name	*Chemical Description*	*Characteristics*
Cocaine		
Coke, snow.....	D-Cocaine HCl and cutting impurities	Not volatile; administered through nasal or intravenous route
Crack, rock, free base.....	Pure alkaloid cocaine	Volatile; can be smoked
Methamphetamine		
Crank, speed....	D-, L-, or D/L-Methamphetamine HCl and impurities	Volatility dependent on impurities
Ice, crystal	D-Methamphetamine HCl (high purity, uncut)	Volatile; can be smoked

HCl = hydrochloride

The popularity of smoked methamphetamine is due to the immediate clinical effects of a euphoria resulting from the drug's rapid absorption from the lungs. Thus, the effect of intravenous use can be achieved without using needles. For several years, patients of one of us (B.H.) have described smoking methamphetamine-HCl powder or crystals by first placing the substance in a piece of metal foil molded into the shape of a bowl and then heating it over the flame of a cigarette lighter. The fumes then can be inhaled through a straw. Because of a more rapid and intense drug effect, these patients described a "high" distinct from that produced by snorting or ingesting methamphetamine. They also reported that smoking the drug produced a high lasting a shorter time than that experienced with other routes of ingestion. As would be expected when methamphetamine is smoked, the duration of action is similar to that produced with intravenous injection.

Clinical Pharmacology

Methamphetamine causes central nervous system (CNS) stimulation that may induce euphoria, increase alertness, intensify emotions, alter self-esteem, and allegedly increase sexuality.[9] At the cellular level, dopamine is displaced from specific nerve terminals, causing hyperstimulation of dopaminergic receptor neurons in the synaptic cleft.[25,26] These hyperstimulated neurons in turn stimulate various CNS pathways and the sympathetic nervous system. Direct peripheral and organ stimulation by methamphetamine may also occur. The half-life of amphetamines ranges from 10 to 30 hours, depending on urine pH.[27,28] Methamphetamine has greater CNS efficacy compared with D-amphetamine, presumably because of increased CNS penetration.[29]

The euphoric effects produced by methamphetamine, cocaine, and various designer amphetamines are similar and may be difficult to differentiate clinically. The findings from many studies in animals and humans support these observations. A distinguishing clinical feature is the longer half-life of methamphetamine, which may be as much as ten times longer than the half-life of cocaine.[16,30] Nevertheless, more recent studies in animals with D-amphetamine and cocaine suggest differences in underlying CNS mechanisms between the two types of stimulants.[31-33]

Because methamphetamine is purchased illicitly and may be mixed with both inert and other toxic substances, the clinical observation of toxic effects is more relevant than an estimate of ingested dose. In addition, tachyphylaxis occurs with methamphetamine use, and long-term users tolerate higher doses with fewer symptoms. Fatalities have been reported after ingestions as low as 1.5 mg per kg of methamphetamine,[34] whereas long-time abusers in whom tolerance to the drug develops may use as much as 5,000 to 15,000 mg per day.

Toxic Effects

In toxic doses, methamphetamine induces unpleasant CNS symptoms such as agitation, anxiety, hallucinations, delirium, and seizures; death can occur.[16,35-37] Cardiovascu-

lar symptoms such as chest pain, palpitations, or dyspnea can also develop. There is evidence that high doses of methamphetamine induce irreversible CNS-destructive changes.[38,39]

Methamphetamine can both induce an acute toxic psychosis in previously healthy persons and precipitate a psychotic episode in those with psychiatric illness.[40] Nearly all patients presenting to emergency departments with toxic effects require referral to a psychiatric center. In the past, psychiatric disorders were diagnosed before addiction in many amphetamine users. This has not been the case recently, however.[41] An acute and dramatic choreoathetoid disorder can also be triggered by amphetamines.[42] Hyperthermia may result from CNS-induced abnormalities, seizures, or muscular hyperactivity. Rhabdomyolysis may occur secondarily.[15]

Cardiovascular manifestations of amphetamine toxicity include hypertension, tachycardia, atrial and ventricular arrhythmias, and myocardial ischemia.[43,44] Chest pain has been reported in some persons but usually without electrocardiographic changes. The incidence of toxicity-induced cardiovascular symptoms is less than with cocaine.

Patients who are unconscious on arrival at an emergency department or who have been found unresponsive may have used methamphetamine. In some of these persons, lack of responsiveness may be due to the use of other drugs such as opiates. Other patients may be unresponsive because of intravenous methamphetamine use. Hypothesized reasons for this effect include seizure, hypotension, a reaction to a contaminant, or undescribed effects of intravenous amphetamine. Other disorders that have been described include cerebrovascular accident due to hemorrhage or vasospasm.[45,46]

Treatment

Despite methamphetamine's ability to induce significant CNS and cardiovascular stimulation, relatively few patients who present to emergency departments for acute intoxication require pharmacologic intervention.[7] In many emergency departments, patients are not treated for agitation unless they could harm themselves while jerking or tearing at their restraints. These hyperactive or agitated persons can be treated with haloperidol or diazepam, and all appear to respond well to treatment with either drug.

Central Nervous System Toxicity

Haloperidol and diazepam are well-established agents that antagonize CNS symptoms. Haloperidol, a dopamine-2 blocking agent, can specifically antagonize the central effects of methamphetamine. Studies in animals have shown the superiority of haloperidol to diazepam in protecting against death.[33] Multiple clinical reports attest to the efficacy of haloperidol.[7,14,15] In addition, on receiving intravenous haloperidol, patients who sustain the acute choreoathetoid syndrome may have symptoms quickly resolve. Haloperidol has an advantage over diazepam in that it can be given intravenously or intramuscularly. Recommended doses are 2.0 to 5.0 mg initially, with additional dosing titrated to clinical response.

Diazepam, a benzodiazepine that enhances γ-aminobutyric acid neurotransmission, affects methamphetamine intoxication through a nonspecific sedative action. Diazepam is highly effective in antagonizing the stimulant toxic effects of cocaine but not amphetamines in animals.[31,33] Despite this observation, diazepam is used successfully to control clinical symptoms.

Cardiovascular Effects

Many antihypertensive agents and β-blockers are effective in reversing methamphetamine-induced cardiovascular symptoms. For treating an amphetamine-induced hypertensive crisis, agents such as phentolamine or nitroprusside provide efficacy. Blood pressures may also respond indirectly to the sedating effects of haloperidol. Calcium channel blockers have been used successfully in some emergency departments.

Many cases of methamphetamine toxicity can be managed conservatively. The clinician should confirm suspected amphetamine use through a urine toxicologic analysis. Other conditions that may produce symptoms—such as infections, metabolic disorders, or use of other drugs—should be excluded. Patients should receive volume replacement as determined by hydration status. In past studies, as few as 10% of the patients presenting to emergency departments required admission, and those who were admitted to hospital were generally discharged within two days. In the past, vital signs were thought to be an indicator of the severity of intoxication, with a temperature above 40°C being a poor prognostic sign. In one series, however, there was no significant difference in vital signs between those admitted and those not admitted.

Summary

In conclusion, methamphetamine is a dangerous drug that matches or supersedes cocaine in inducing symptoms of euphoria. The volatility of methamphetamine appears similar to that of crack cocaine, and thus it can compete with cocaine for use by long-term or recreational users wanting a rapid high through inhalation. Unlike that of cocaine, the half-life of methamphetamine may produce exceptionally long-lasting toxic effects. Clinicians should consider the possibility of methamphetamine use or abuse in any patient presenting with psychosis, violence, seizures, or cardiovascular abnormalities.

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